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Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison

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ABSTRACT

Background: Severe asthma is a heterogeneous disease. Patients with both eosinophilic and allergic asthma phenotypes may be eligible for treatment with mepolizumab and omalizumab. Evidence on the relative effectiveness of these treatments in this 'overlap' population would be informative for clinical and payer decision making.

Methods: A systematic literature review and indirect treatment comparison (Bayesian framework) were performed to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-ons to standard of care. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving high-dose inhaled corticosteroids plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (Overlap population) and 2) either treatment (Trial population).

Results: In the Overlap population, no differences between treatments in clinically significant exacerbations and exacerbations requiring hospitalization were found, although trends favored mepolizumab (rate ratio [RR]:0.66 [95% credible intervals (CrI):0.37,1.19]; 0.19[0.02,2.32], respectively). In the Trial population, mepolizumab treatment produced greater reductions in clinically significant exacerbations (RR:0.63 [95% CrI:0.45,0.89]) but not exacerbations requiring hospitalization compared with omalizumab (RR:0.58 [95% CrI: 0.16,2.13]), although the trend favored mepolizumab. Both treatments had broadly comparable effects on lung function, and similar tolerability profiles.

Conclusions: Whilst this analysis has limitations due to a restricted evidence base and residual heterogeneity, it showed that in patients with severe asthma, mepolizumab seems to be at least as effective as omalizumab and that the tolerability profiles of the two treatments did not meaningfully differentiate.

1. Introduction

Severe asthma is characterized by frequent exacerbations, hospitalizations and poor symptom control, despite the regular use of intensive maintenance therapies [1,2]. Severe asthma is a heterogeneous disease with several phenotypes, including allergic and/or persistent eosinophilic asthma [2,3]. Owing to the significant unmet need in this patient population, novel targeted therapies have been developed for different phenotypes of severe asthma, with the aim of reducing the rate of clinical exacerbations [4]. For example,

Abbreviations: Crl, credible interval; HRQoL, health related quality of life; ITC, indirect treatment comparison; MEPO, mepolizumab; OCS, oral corticosteroid; OMA, omalizumab; RCT, randomized controlled trial; RR, rate ratio; SoC, standard of care; SCS, systemic corticosteroid.

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mepolizumab (GSK, London, UK) is an anti-interleukin (IL)-5 mAb approved as an add-on treatment in patients with severe eosinophilic asthma [5,6]; omalizumab (Genentech, Inc., South San Francisco, CA), an anti-immunoglobulin E (IgE) monoclonal antibody (mAb) [7–9] is licensed as an add-on treatment for patients with moderate-to-severe (US) or severe (EU) allergic asthma.

In clinical trials, both mepolizumab and omalizumab were efficacious at reducing exacerbation rates in their respective patient populations when compared with placebo [10–13]. It is estimated that approximately one third of patients with severe asthma who are eligible for treatment with one biologic (mepolizumab or omalizumab) may also be eligible for treatment with the other biologic, hence for these patients the clinician has to make a choice between mepolizumab and omalizumab treatment [14,15]. Information on the relative effectiveness and tolerability profiles of the two treatments in this 'overlap' population would therefore be useful for both clinical and payer decision making. Since there are currently no published comparisons of mepolizumab and omalizumab in patients with severe asthma, we conducted a systematic literature review and indirect treatment comparison (ITC) to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care (SoC), in patients with severe asthma.

2. Methods

2.1. Data sources

A systematic literature review was conducted on August 5, 2014, and updated on July 8, 2015, to identify published randomized controlled trials (RCTs) of mepolizumab or omalizumab in severe asthma (GSK ID: HO-14-13436). Further details of the search strategy including databases and search terms can be found in Supplementary Appendix A. This was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines based on a pre-defined PICOS (Population; Intervention; Comparator; Outcomes; and Study Design) framework.

The main objective of this systematic literature review was to collect all publicly available RCTs to support an ITC of mepolizumab and omalizumab in severe asthma. Due to the broad evidence base of severe asthma studies and the clinical and methodological heterogeneity, further pre-defined PICOS inclusion and exclusion criteria were applied to the studies identified from the systemic literature review to generate the evidence base for the ITC analysis (GSK ID 200277/HO-13-9058). The quality of RCTs was evaluated based on criteria outlined in Supplementary Appendix A and the results of this assessment are shown in Table S1. The additional ITC eligibility criteria imposed a minimum appropriate level of comparability among the studies.

2.2. Eligibility criteria for inclusion in the indirect treatment comparison

2.2.1. Population

In order to be included in this ITC, studies were required to enroll patients meeting the following criteria: ≥12 years of age, with severe asthma (patients receiving ≥1000 μg/day beclomethasone dipropionate equivalent plus ≥1 additional controller, and with a documented history of exacerbations). This population definition was then further refined to incorporate treatment eligibility for mepolizumab and omalizumab, as far as data availability allowed. Two populations were defined, 1) the Overlap population, which aimed to include patients eligible for both mepolizumab AND omalizumab, and 2) the Trial population, which aimed to include patients eligible for either mepolizumab OR omalizumab (Table 1).

Mepolizumab eligibility was defined as severe eosinophilic asthma (blood eosinophil count ≥150 cells/μL at treatment initiation or ≥300 cells/μL in the prior 12 months) and a history of exacerbations. Omalizumab eligibility was defined as allergic asthma with a pre-treatment serum IgE versus body weight combination that met EU omalizumab prescribing criteria (baseline IgE levels ≥30–≤1500 IU/mL [patients ≥12 years of age with IgE <76 IU/mL should have unequivocal *in vitro* reactivity to perennial allergen]; weight ≥20 kg–≤150 kg; maximum dose 600 mg subcutaneous [SC] every 2 weeks). Detailed study and population inclusion criteria are shown in Table 1 and Fig. S1.

In order to accurately identify the Overlap population, treatment eligibility criteria would need to be applied to individual patient-level data from all included studies. However, patient-level data were only available for the mepolizumab studies. Therefore, it was necessary to make an assumption that patients enrolled in omalizumab trials that met the disease severity criteria also fulfilled the eligibility requirements for mepolizumab. However, the omalizumab RCTs identified by the systematic literature review had lower or undefined exacerbation history requirements, compared with a requirement for at least 2 exacerbations in the previous year in the mepolizumab RCTs. Consequently, if the exacerbation history requirement had been set to ≥2 exacerbations in the previous year, all the omalizumab trials would have been excluded from the analyses. Therefore, the exacerbation history requirement was relaxed in the Overlap population when compared with the inclusion criteria in the mepolizumab RCTs, while remaining strict enough to help identify mepolizumab and omalizumab eligible RCT populations of similar disease severity (according to exacerbation history).

2.2.2. Intervention

Eligible interventions for inclusion in the ITC were mepolizumab 100 mg SC and omalizumab as per the EU prescribing criteria. Detailed study and population inclusion criteria are shown in Table 1 and Fig. S1.

2.2.3. Comparator

It was anticipated that the common comparator for mepolizumab and omalizumab, would be placebo, in addition to SoC. If eligible studies examined omalizumab versus SoC alone, the SoC alone data were combined with placebo in the meta-analysis (ie., treated as a single common comparator for the active interventions). This was considered necessary due to the very small number of studies expected to be otherwise eligible for the ITC.

2.2.4. Outcomes

The primary pre-specified endpoints were the rate of clinically significant exacerbations (defined as exacerbations requiring systemic corticosteroid [SCS] treatment or at least a doubling of existing dose for maintenance oral corticosteroid [OCS] and/or hospitalization and/or an emergency department visit) and the rate of exacerbations requiring hospitalization. Pre-specified secondary endpoints included the change from baseline in health-related quality of life (HRQoL), measured by the St George's Respiratory Questionnaire or Asthma Quality of Life Questionnaire; change from baseline in lung function, defined as % predicted pre-bronchodilator forced expiratory volume in 1 s (FEV_1), or post-bronchodilator FEV_1, or FEV_1% predicted, or morning peak expiratory flow (PEF; L/min) when these data were unavailable; change from baseline in asthma control measured by the Asthma Control Questionnaire; and the proportion of patients with any adverse events (AEs), serious AEs (SAEs), withdrawals due to AEs or fatal